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PRE-APPEAL BRIEF REQUEST FOR REVIEW

Docket Number (Optional)
034547-0112

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On December 12, 2006

Signature

Typed or printed name

Application Number	Filed
09/402,488	04/23/1998
First Named Inventor	
Maurice MOLONEY	
Art Unit	**Examiner**
1656	David J. Steadman

Applicant requests review of the final rejection in the above-identified application. No amendments are being filed with this request.

This request is being filed with a notice of appeal.

The review is requested for the reason(s) stated on the attached sheet(s).
Note: No more than five (5) pages may be provided.

I am the

☐ applicant/inventor.

Courtenay C. Brinckerhoff
Signature

☐ assignee of record of the entire interest.
See 37 CFR 3.71. Statement under 37 CFR 3.73(b) is enclosed. (Form PTO/SB/96)

Courtenay C. Brinckerhoff
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Registration number if acting under 37 CFR 1.34

December 12, 2006
Date

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below*.

☒ *Total of 1 forms are submitted.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appl. No	:	09/402,488	Confirmation No.:	6010
Docket No.	:	9369-98	Customer No.:	001059
Applicant	:	Maurice M. Moloney, *et al.*		
Filed	:	February 16, 2000		
Title	:	Method for Producing and Cleaving a Fusion Protein With an N-Terminal Chymosin Pro-Peptide (Amended)		
TC./A.U.	:	1652		
Examiner	:	David J. Steadman		

PRE-APPEAL BRIEF REQUEST FOR REVIEW

Mail Stop AF
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Applicant hereby requests pre-appeal brief review of the rejections pending in the captioned application. A Notice of Appeal and the required fees are submitted herewith.

REMARKS

Claims 1, 4-10, 12-16, 18-19, 50 and 51 are pending and stand finally rejected on the following grounds: (i) alleged new matter of a "non-human" host cell, under 35 U.S.C. § 112, ¶1 (claims 1, 4-10, 12-16, 18-19 & 50); (ii) alleged lack of enablement of recombinant protein production in animals and plants, under 35 U.S.C. § 112, ¶1 (all claims); and (iii) alleged obviousness over Ward in view of Walsh and Yonezawa, under 35 U.S.C. § 103(a) (claims 1, 4, 6-9, 13, 15, 19 and 51), further in view of Fine (claim 5) or Dunn (claims 14 and 50). Applicant believes that these rejections are based on clear errors, as outlined below.

(i) New Matter Rejection of Claims 1, 4-10, 12-16, 18, 19, 50 and 51

The claims are rejected for allegedly containing new matter in the recitation of a "non-human" host cell. This rejection is based on clear error in the Examiner's application of 35 U.S.C. § 112 and in his misinterpretation of the relevant MPEP provisions.

The "fundamental factual inquiry" for written description "is whether the specification conveys with reasonable clarity to those skilled in the art that, as of the filing date sought, applicant was in possession of the invention as now claimed." *See* MPEP § 2163. The instant specification provides ample support for the recitation of a "non-human host cell," and clearly conveys to the skilled artisan that Applicant had possession of the claimed invention at the time of filing. For example, the specification (page 7, lines 3-4) teaches that bacterial cells, insect cells, yeast cells, plant cells and mammalian cells are suitable as host cells. At page 13, lines 27-29, the specification additionally teaches that the protein "may also be produced in an edible food source, such as animal milk, or in an edible crop." Applicant respectfully submits that these teachings, particularly when read in view of the disclosure as a whole, plainly convey to the skilled artisan Applicant's possession of the invention with regard to non-human host cells. Indeed, because aspects of the invention relate to "methods for recovering recombinantly produced polypeptides," *see, e.g.*, specification at page 1, lines 3-4 4, and abstract), those skilled in the art surely would understand that references to "mammalian" host cells includes "non-human" host cells, especially given the reference to production in "animal milk."

The Examiner cites the MPEP for the proposition that "[i]f alternative elements are positively recited in the specification, they may be explicitly excluded in the claims," and notes that there is "no such positive disclosure of . . . production using a 'human' host cell." Advisory Action of November 7, 2006, at page 4. Yet the cited MPEP passage, while providing an *example* of how a negative limitation might be supported by a positive disclosure, does not purport to advance the *only* way to support a negative limitation. As noted in MPEP § 2173.05(i), "a lack of literal basis in the specification for a negative limitation may not be

sufficient to establish a *prima facie* case for lack of descriptive support." Here the Examiner has not provided "reasons why a person skilled in the art at the time the application was filed would not have recognized that the inventor was in possession of the invention as claimed in view of the disclosure of the application as filed." *See* MPEP § 2163.04. Thus, the instant written description rejection amounts to the imposition of an *in haec verba* requirement, in contravention of PTO rules. Precisely because such a requirement is contrary to law, the present rejection of claims 1, 4-10, 12-16, 18-19 and 48-50 is based on clear error and should be withdrawn.

(ii) Enablement Rejection of Claims 1, 4-10, 12-16, 18, 19, 50 and 51

The claims are rejected for alleged lack of enablement with respect to the recombinant production of proteins in animals and plants. This rejection is based on clear error in the Examiner's application of the enablement requirements of 35 U.S.C. § 112.

Faced with the evidence cited at pages 8-11 of the Response of April 21, 2006 demonstrating recombinant protein in animal hosts (5 publications), bacterial hosts (1 publication), insect hosts (3 publications), and plant hosts (5 publications),the Examiner finds "no dispute that methods for producing transgenic animals and plants were known . . . at the time of the invention." Nevertheless, he continues to question enablement with respect to recombinant protein production in "any non-human host" or in "any plant." November 7th Advisory Action, page 5. So doing, the Examiner cites publications alleged to evidence unpredictability in the art of protein expression in certain animal hosts. But, as Applicant demonstrated at pages 10-12 of the Response of October 11, 2006, the cited references -- Dyck, Vain, and Potrykus -- actually support Applicant's position, because they evidence the advanced state of the art and address issues that have arisen with the commercialization of recombinant protein production.

In a further attempt to prop up the enablement rejection, the Examiner cites two new references, Sang and Mozdziak, in the latest Advisory Action, but these also fail to support the

enablement rejection. Both Sand and Mozdziak report on progress made in creating transgenic chickens, including successful experimental approaches to this end. *See, e.g.,* Sang, page 1185 ("The preliminary results on [retroviral] transgene expression in several generations . . . indicate that transgene expression will be reproducible . . . ."); Mozdziak, page 416 ("Retroviral gene transfer techniques have been used the most frequently to generate transgenic chickens . . . ."). Moreover, neither reference indicates that it would take an undue amount of experimentation to achieve recombinant protein production in a chicken host; rather, their focus is on generating stable lines of transgenic chickens for research and commercial use. Thus, neither Sand nor Mozdziak supports the enablement rejection.

The weight of the evidence of record, including that of the specification and the evidence cited at pages 8-11 of the April 21 Response, at pages 10-12 of the October 11 Response, and on pages 10-13 of the Response of September 12, 2006, supports the enabled quality of the claimed invention. Thus, the enablement rejection should be withdrawn.

(iii) Obviousness Rejection of Claims 1, 4-9, 13, 15, 19 and 51

The obviousness rejections of claims 1, 4, 6-9, 13, 15, 19 and 51 over Ward in view of Walsh and Yonezawa, of claim 5 over the same primary references further in view of Fine, and of claims 14 and 50 over the same primary references further in view of Dunn, improperly rest on a hindsight reconstruction of the invention. In this instance, the cited references fail to provide any suggestion or to evidence a motivation that would lead the skilled artisan to the present invention, or that would provide any reasonable expectation of success along these lines.

Ward describes a nucleic acid encoding a fusion protein that includes a bovine chymosin prosequence as a cleavable linker. The reference provides no specific teachings of how to cleave the bovine chymosin prosequence from its fusion protein. Walsh discloses the use of a bovine k-casein sequence that is sensitive to chymosin cleavage as a cleavable linker for fusion proteins, but does not teach or suggest the use of a chymosin pro-peptide for such a purpose. Yonezawa

reports the various cleavage sites for several chromogenic chymosin substrates. Thus, the Examiner has not cited any prior art that suggests the use of a mature form of an autocatalytically maturing aspartic protease to cleave a chymosin pro-peptide from a fusion protein comprised of a heterologous protein, as presently claimed.

Applicant has demonstrated that those skilled in the art had no reasonable basis for expecting that an aspartic protease would be capable of cleaving a chymosin pro-peptide from a fusion protein to release the recombinant polypeptide and that, without an assurance of accurate cleavage,[1] there was no motivation to have employed an aspartic protease as presently claimed. *See, e.g.,* April 21 Response, pages 11-15; Moloney Declaration submitted April 21, 2006, ¶ 4-11; Response of October 25, 2005, pages 7-11; Response of September 8, 2005, pages 8-12.

The latest Advisory Action alleges that the skilled artisan "would have had a reasonable expectation of success that chymosin can cleave its own fusion protein," but the invention does not involve cleavage of chymosin's "own fusion protein." Instead, the claimed methods involve cleavage of a fusion protein comprising a recombinant polypeptide that is heterologous to the chymosin pro-peptide, a method that is not suggested by the cited references.

Thus, the instant obviousness rejections are clearly erroneous, and should be withdrawn.

Respectfully submitted,

Date December 12, 2006

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[1] The Examiner is incorrect to the extent the he does not interpret the instant claims to recite accurate cleavage. Step (d) of claim 1 recites the release of "said recombinant polypeptide," thus specifying accurate cleavage of the recombinant polypeptide from the fusion protein. *See also* Claim 51, last line.